Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 1-10, 22-30, 43-62, 64-68, 73-109 and 138 are pending in the application, with claim 1 being the independent claim. Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Oath/Declaration

The Office Action stated that the oath or declaration is allegedly defective because the oath/declaration does not acknowledge the priority to provisional applications. Office Action, page 2. Applicants point out that specific reference claiming the benefit of a prior provisional application should appear in the first sentence of the specification and/or in an application data sheet. M.P.E.P. § 201.11(III)(B); 37 C.F.R. § 1.78(a)); 37 C.F.R. § 1.76. The oath or declaration need only indicate priority to a *foreign* application unless the foreign priority information is supplied on an application data sheet. M.P.E.P. § 602; 37 C.F.R. § 1.76. Applicants' claim to benefit of prior provisional applications has been made in the first sentence of the specification. Thus, Applicants' oath/declaration is not defective and priority to prior provisional applications has been properly made. Accordingly, Applicants respectfully request that this objection be withdrawn.

Objection to the Specification

The Office Action objected to the disclosure because SEQ ID NOs are missing at paragraphs 261, 289 and 291. Office Action, page 3. Applicants have amended paragraphs 261, 289 and 291 to include SEQ ID NOs. Accordingly, Applicants respectfully request that this objection be withdrawn.

Rejections under 35 U.S.C. § 112

Claims 1-10, 22-30, 43-62, 64-68, 73-88 and 138 were rejected under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the written description requirement. Office Action, page 4. Applicants respectfully traverse the rejection.

It was alleged that the phrase "wherein said cell death is not the result of a cytotoxic T lymphocyte induced lytic event" within claim 1 is not clearly supported in the specification and the claims as originally filed. Office Action, page 4. The test for written description requirement is whether one skilled in the art can reasonably conclude that the inventor has possession of the claimed invention in the specification as filed. *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563, 19 U.S.P.Q.2d 1111, 1116 (Fed. Cir. 1991); M.P.E.P. § 2163.02. The Federal Circuit recently reemphasized the well-settled principle of law that "[t]he written description requirement does not require the applicant 'to describe exactly the subject matter claimed, [instead] the description must clearly allow persons of ordinary skill in the art to recognize that [they] invented what is claimed.'" *Union Oil of Cal. v. Atlantic Richfield Co.*, 208 F.3d 989, 997 (Fed. Cir. 2000) (quoting *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989)). Furthermore, an applicant is not required to explicitly describe the subject

matter. *See Unocal*, 208 F.3d at 1000; *see also* M.P.E.P. § 2163.02 ("The subject matter of the claim need not be described literally (i.e., using the same terms or *in haec verba*) in order for the disclosure to satisfy the description requirement."). The court emphasized the importance of what the person of ordinary skill in the art would understand from reading the specification, rather than whether the specific embodiments had been explicitly described or exemplified. *See id.*

Applicants assert that the specification provides support for the phrase "wherein said cell death is not the result of a cytotoxic T lymphocyte induced lytic event." Specifically, in paragraph [0373] on page 73, the specification notes that the selection methods described in the specification include one or a combination of modifications, uses and other embodiments described, and also provide for the *exclusion* of any one or more modifications, uses and other embodiments. The specification continues by stating that one selection method corresponds to a method of direct selection which *excludes CTL-mediated immunity*. *See* Specification, paragraph [0373]. In CTL-mediated immunity, CTLs (cytoxic T lymphocyctes) function by destroying a cell, often as a result of cell lysis. *See Essential Immunology*, ed. Ivan M. Roitt, pg. 28-32. (7^{th} Ed. 1991). A selection method which excludes CTL-mediated immunity is thus a selection method which excludes destruction of the cell (*i.e.* cell death) as a result of a CTL-induced lytic event.

Furthermore, the specification provides explicit support for the phrase "cytotoxic T lymphocyte induced lytic event." In paragraph [0136], for example, the specification explicitly states that in one embodiment of the invention, cell death can be the result of a cytotoxic T-lymphocyte induced lytic event. *See* Specification, paragraph [0136]. Thus,

based on the arguments presented above, Applicants assert that the phrase "wherein said cell death is not the result of a cytotoxic T lymphocyte induced lytic event" is adequately described. Accordingly, Applicants have reasonably conveyed to one skilled in the art that they had possession of the claimed invention. Applicants respectfully request that the rejection be reconsidered and withdrawn.

Claims 1-10, 22-30, 43-62, 64-68, 73-88 and 138 were rejected under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the written description requirement. Office Action, page 4. The Office Action alleged that the "specification has not disclosed the use of any type of host cells in the method of screening for a target polypeptide whose expression promotes cell death, and the cell death is not the result of a cytotoxic T lymphocyte induced event." Office Action, page 5. It was further alleged that "the claimed invention contains no identifying characteristics regarding the identified polynucleotide or the host cells or the library of insert polynucleotides used. Additionally, the narrow scope of examples directed to the use of specific host cells (host cells contain cell death domain receptor) and vaccinia virus vectors, which are clearly not representative of the scope of the presently claimed method." Office Action, page 6. Applicants respectfully disagree and traverse the rejection.

Identifying Characteristics of the Host Cell

The Federal Circuit stated in *Univ. of Calif. v. Eli Lilly & Co.*, 43 U.S.P.Q.2d 1398 (Fed. Cir. 1997), that:

> A description of a genus of cDNAs may be achieved by means of a recitation of [1] *a representative number of cDNAs,* defined by nucleotide sequence, *falling within the scope of the genus* ...[w]e will not speculate

> in what other ways a broad genus of genetic material may be properly described . . . .

Univ. of Calif., 43 U.S.P.Q.2d at 1406 (emphasis added).

Applicants note that independent claim 1 is directed to a method of selecting a target polynucleotide, comprising introducing a library of insert polynucleotides into a population of *mammalian* host cells, where at least one of the insert polynucleotides comprises the target polynucleotide, where the library is constructed in a poxvirus vector, an adenovirus vector or a herpesvirus vector, and where expression of the target polynucleotide directly or indirectly promotes host cell death.

Applicants assert, contrary to the Examiner's position, that the specification discloses a representative number of species which fall within the scope of the genus and are adequately described. Applicants point out, as the Office Action has indicated, that the specification describes specific host cells. Office Action, page 5. One of these cells corresponds to the murine myelomonocytic cell line RAW. Specification, [0382] (page 76). Additionally, the specification discloses numerous other species of *mammalian* host cells for use in the claimed invention. For example, the specification describes examples of host cells which include the following: monkey kidney CVI line transformed by SV40; human embryonic kidney line; baby hamster kidney cells; chinese hamster ovary-cells-DHFR; mouse sertoli cells; monkey kidney cells; african green monkey kidney cells; human cervical carcinoma cells; canine kidney cells; buffalo rat liver cells; human lung cells; human liver cells; mouse mammary tumor; TRI cells; human B cells; human T cells (MOLT-4, ATCC CRL 1582); and human macrophage cells. Specification, paragraph [0380] (page 75). Other examples of cell types are described in paragraphs

[0510]-[0511] (pp. 116-117) and paragraph [0538] (pp.126-127). The specification thus provides a representative number of mammalian host cells which can be used in the claimed method.

Furthermore, any mammalian cell line which can be transfected with the vectors of the claims (*i.e.* poxvirus, adenovirus or herpesvirus) can be used. These types of cell lines are known in the art, and numerous examples are given in the application.

Thus, the specification discloses numerous examples of mammalian host cells which can be used in a method of screening for a target polypeptide whose expression promotes cell death, and the cell death is not the result of a cytotoxic T lymphocyte induced event. In fact, the specification, while disclosing that RAW cells (murine myelomonocytic cells) can be transfected with a suicide gene construct in order to identify target polynucleotides, also notes that *similarly responsive cells* can also be utilized to carry out Applicants claimed method. Specification, [0483] (page 107). Thus, under the reasoning of *Eli Lilly*, the present application adequately describes the claimed genus of "mammalian" host cells.

Recently, the Federal Circuit specifically examined the written description requirement in the context of a claim including the term "host cells." *See Amgen Inc. v. Hoechst Marion Roussel Inc.*, 314 F.3d 1313 (Fed. Cir. 2003). In *Amgen*, the claims at issue recited "vertebrate" host cells and "mammalian" host cells, identified as types of cells in which the EPO protein could be expressed. Where the specification only disclosed two examples of host cells, CHO and COS-1, the Federal Circuit stated,

> when used, as here, merely to identify types of cells . . . ., the words "vertebrate" and "mammalian" readily "convey[ ] distinguishing

> information concerning [their] identity" such that one of ordinary skill in the art could "visualize or recognize the identity of the members of the genus."

Amgen, 314 F.3d 1313, 1332 (citing *Eli Lilly*).

Thus, the Federal Circuit in *Amgen* concluded that *Eli Lilly* did not strictly apply and that the claim term "mammalian host cell" was adequately described even when *only two species* within the genus were disclosed.

In the present case, similar to that in *Amgen*, Applicants' claim includes the term "mammalian host cell" in order to identify what type of cell the isolated target polynucleotide will be expressed. Applicants describe many species which fall within the genus. Thus, applying the written description test of either *Eli Lilly* or *Amgen*, Applicants have reasonably conveyed to one skilled in the art that they have possession of the claimed invention. Thus, the written description requirement has been satisfied. Accordingly, Applicants respectfully request that the rejection be reconsidered and withdrawn.

Identifying Characteristics of the Target Polynucleotide

Identifying characteristics of a target polynucleotide are presented in the description of the method by which a target polynucleotide is selected. *See* Specification, paragraphs [0366] - [0399]. For example, one method of selecting a target polynucleotide is to select the nucleotide based on an altered phenotype, such as cell viability (cell death). *See* Specification, paragraphs [0368] - [0369]. This altered phenotype can then be measured by methods known in the art and described in the specification. *See* Specification, paragraphs [0370] - [0371].

In one embodiment of the method described above, the target polynucleotide is selected based on its induction of a suicide gene construct. *See* Specification, paragraph [0455]. Polynucleotides which are useful as suicide genes include p53, certain toxic sequences (including, *inter alia*, diphtheria A chain, ricin A chain, abrin A chain, modeccin A chain, alpha-sarcin, etc.) and cell death-inducing sequences. *See id.* Therefore, a target polynucleotide of the claimed invention can correspond, for example, to a polynucleotide which functions in the pathway of p53 which is associated with cell death. Similarly, a target polynucleotide can correspond to a polynucleotide which functions in the pathway of other suicide gene products listed above. Thus, the specification discloses characteristics of a target polynucleotide which may be identified by the claimed method.

Identifying Characteristics of the Library

Applicants again point out that the test for written description requirement is whether one skilled in the art can reasonably conclude that the inventor has possession of the claimed invention in the specification as filed. *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563, 19 U.S.P.Q.2d 1111, 1116 (Fed. Cir. 1991); M.P.E.P. § 2163.02. Applicants assert that the library of Applicants' claimed method is adequately described.

The present claims are directed to a method of selecting a polynucleotide from a library constructed in a particular viral vector and expressed in mammalian host cells, by culturing the host cells under conditions allowing expression of the insert polynucleotides, and collecting insert polynucleotides from those host cells which undergo cell death.

The specification on pages 65-68 describes the production of a library using the poxvirus vector, vaccinia virus. *See* Specification, paragraphs [0352] to [0361]. The description regarding the production of this vaccinia virus library includes disclosure related to introducing the library of insert polynucleotides into a population of host cells and culturing the host cells under conditions such that the insert polynucleotides are expressed. *See id.* The specification also describes the use of vaccinia virus vector, comprising the tri-molecular recombination method.

Additionally, the specification discloses other types of libraries and provides identifying characteristics of these libraries. For example, the specification describes the production of a herpesvirus library of the claimed method. Specification, [0362] (pages 68-69). The specification discloses that a polynucleotide library can be constructed in a herpesvirus amplicon vector which could be packaged into a library of infectious amplicon particles. Such a library could be employed in the indirect or direct selection methods (*e.g.*, lethality/adherence based selection methods) of this invention. *See id.*

Furthermore, the specification describes the production of an adenovirus library of the claimed method. Specification, [0363] (pages 69-70). The specification discloses methods for the production of recombinant adenovirus (Miyake, S. *et al.*, *Proc. Natl. Acad. Sci. USA* 93:1320-1324 (1996); He, T.C. *et al.*, *Proc. Natl. Acad. Sci. USA* 95:2509-2514 (1998)) and notes that such an adenovirus library could be employed in the direct and indirect selection methods of this invention. *See id.*

Thus, the specification discloses and identifies characteristics regarding libraries and vectors (vaccinia virus, herpesvirus and adenovirus) of the claimed method.

Working Examples

Finally, the Examiner states that no working examples of the instantly claimed method have been described. Office Action, page 5-6. Applicants note that a requirement of "working examples" is an incorrect application of the law with respect to the written description requirement. The written description requirement is met if the specification discloses relevant identifying characteristics sufficient to describe the claimed invention in such terms that a skilled artisan would recognize that the applicant was in possession of the claimed invention. *See* M.P.E.P. § 2163(II)(A). Based on the comments in the sections above, Applicants assert that the disclosure adequately describes the claimed method and that the written description requirement has been satisfied. Accordingly, Applicants respectfully request that this rejection be reconsidered and withdrawn.

Rejections under 35 U.S.C. § 102(b)

Claims 1-10, 22-30, 43, 60, 62, 64-71 and 76-79 were rejected under 35 U.S.C. § 102(b) as allegedly anticipated by U.S. Patent No. 5,712,115 to Hawkins *et al.* [hereinafter "Hawkins"]. Office Action, page 7. Applicants respectfully traverse this rejection.

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987); M.P.E.P. § 2131.

The present claims are directed to a method of selecting a polynucleotide from a library constructed in a particular type of viral vector and expressed in mammalian host cells, culturing the host cells under conditions allowing expression of the insert polynucleotides, and collecting insert polynucleotides from those host cells which undergo cell death.

The Office Action states that the Hawkins reference discloses that the nucleotide sequence encoding CDAP is inserted into an appropriate expression vector and that a variety of expression vector/host systems may be utilized to contain and express a CDAP protein. Office Action, page 9. The Office Action continues by stating that Hawkins teaches mammalian host cells and viral expression systems (in column 11). *See id.* Applicants point out that that information in column 11 of Hawkins does not disclose expression of a *library* using mammalian host cells and viral expression systems. Hawkins only discloses that an adenovirus vector can be utilized to express the *CDAP sequence* and that this *CDAP expression construct* can be expressed in mammalian host cells.

The Office actions states that Hawkins discloses any number of selection systems which may be used to recover transformed cell lines and points to column 12 where host cells which contain the coding sequence for CDAP and express CDAP may be identified. The Office Action alleges that this disclosure in Hawkins refers to the selection method of the instant claims. *See id.* Applicants respectfully disagree. Applicants point out that Hawkins, in column 12, only discloses the selection and isolation of cells lines which express *CDAP*, but does not disclose selection of cell lines transformed with a *library*.

Finally, the Office action states that Hawkins, in column 13, teaches that host cells transformed with a *CDAP* nucleotide sequence may be cultured under conditions suitable for the expression and recovery of the encoded protein from cell culture. Again, Applicants point out that Hawkins, in column 13, only discloses the culturing of cell lines which express *CDAP*, but does not disclose culturing of cell lines which express a *library* of polynucleotides. Thus, Hawkins does not teach each and every element as set forth in the claimed invention.

Applicants note that Hawkins does not teach construction of a library in a viral vector which is an element of Applicants' claimed invention. Hawkins only discloses the construction of a phagemid library which could be transfected into *E. coli* host cells. *See* Hawkins, Example II, col. 23-24. Hawkins also does not disclose the construction of a library in mammalian cells which is an element of Applicants' claimed method. Hawkins only discloses a library which was constructed in *bacterial cells*. Finally, Hawkins does not does not disclose a selection method, which is an element of Applicants' claimed invention. Hawkins only discloses the random isolation of cDNA inserts from a human rheumatoid synovium library, one of which, when sequenced, was found to encode the protein CDAP (Example II, col. 23-24). The disclosure of Hawkins fails to teach or suggest a general selection method whose purpose is to isolate target polynucleotides which induce cell death in the host cell upon introduction and expression of the target polynucleotide.

Because the Hawkins disclosure fails to teach or suggest all elements of the claimed invention, the present claims are novel over Hawkins. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

Rejections under 35 U.S.C. § 102(e)

Claims 1-10, 22-30, 43-62, 64-88, and 138 were rejected under 35 U.S.C. § 102(e) as allegedly anticipated by US 2003/0133917 A1 (Zauderer). Office Action, page 10. The Office Action states that support for the newly claimed limitation has not been found in the originally filed specification or the claims and that the rejection will be withdrawn in the event that Applicants show support for the newly added claim limitation. Office Action, page 11.

Applicants assert, as noted above, that the specification provides explicit support for the newly added claim limitation "wherein said cell death is not the result of a cytotoxic T lymphocyte induced lytic event" in paragraph [0373] on page 73. The specification explicitly states that the selection method may include a direct selection method which excludes CTL-mediated immunity. *See* Specification, paragraph [0373]. Because support for the newly added claim limitation is in the originally filed specification, Applicants respectfully request that the rejection be reconsidered and withdrawn.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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